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(54) **Title:** COMPOUNDS AND METHODS TO INCREASE ANTI-P-GLYCOPROTEIN ACTIVITY OF BAICALEIN BY ALKYLATION ON THE A RING

Table 3. Anti-P-gp activity and cytotoxicity of alkylated baicalein compounds.

	functional group				c log P[a]	anti-P-gp activity[b]		cytotoxicity (IC_{50} μM)	
compd	R5	R6	R7	R8		EC_{50} (μM)[d]	A_{max}[c]	KB	KD/MDR
control							0.5±0.1[f]		
CSA					2.9	1.2±0.3	3.5±0.3	0.6±0.2	1.5±0.7
VRM					4.5	14±1.2	2.2±0.1	19.6±2.7	51.7±4.7
1	OH	OH	OH	H	3.0	41±5.1	1.7±0.1	62.3±3.7	87.1±3.6
8	OH	OMe	OMe	H	3.5	4.6±1.1	3.4±0.3	> 100	>100
6	OMe	OMe	OMe	H	2.9	5.5±0.4	2.7±0.2	85.9±7.8	57.9±5.9
19	OH	OCH_2O		H	3.7	6.5±1.3	1.2±0.1	> 100	>100
20	OMe	OCH_2O		H	3.1	4.4±2.1	1.5±0.1	> 100	>100
32	OH	OEt	OH	H	3.6	2.3±0.3	3.5±0.3	24.6±3.5	17.5±5.6
38	OH	OEt	OMe	H	4.1	1.5±0.3	2.3±0.2	> 100	>100
33	OH	OEt	OEt	H	4.6	1.8±0.2	4.9±0.2	> 100	>100
44	OMe	OEt	OEt	H	3.9	1.1±0.1	4.2±1.1	81.7±7.8	79.2±5.8
17	OH	OPr	OH	H	4.1	2±0.7	4.7±0.1	58.9±6.3	>100
21	OH	OPr	OMe	H	4.6	1.2±0.4	4.6±0.1	> 100	>100
22	OMe	OPr	OMe	H	3.9	1.7±0.1	4.6±0.1	>100	>100
18	OH	OPr	OPr	H	5.6	1.4±0.4	5.0±0.2	> 100	>100
23	OMe	OPr	OPr	H	5.0	0.9±0.1	5.2±0.1	86.4±6.3	93.7±2.2
45	OH	OC_4H_9	OC_4H_9	H	6.7	1.5±0.3	3.2±0.1	> 100	>100
46	OMe	OC_4H_9	OC_4H_9	H	6.1	1.6±0.2	4.4±0.1	> 100	>100
40	OH	OC_5H_{11}	OC_5H_{11}	H	7.8	1.8±0.1	1.1±0.1	> 100	>100
41	OMe	OC_5H_{11}	OC_5H_{11}	H	7.1	1.5±0.1	3.2±0.1	75.4±6.4	82.6±8.4
42	OH	OC_6H_{13}	OC_6H_{13}	H	8.8	1±0.1	1.0±0.1	> 100	>100
43	OMe	OC_6H_{13}	OC_6H_{13}	H	8.2	1.3±0.2	1.1±0.1	39.1±8.5	44.8±7.9
34	OH	OC_9H_{17}	OC_9H_{17}	H	10.9	7.4±4.1	1.2±0.1	> 100	>100

Me = methyl, Et = ethyl, Pr = *n*-propyl and Ph = phenyl.

(57) **Abstract:** The present invention is directed to analogs of baicalein according to formula (I): where R^5 is H, (C_1-C_{12})alkyl, (C_2-C_{13})acyl, or an optionally substituted phenyl or benzyl group, an acyl group, a C_1-C_{20} alkyl or ether group, a phosphate, diphosphate, triphosphate or phosphodiester group; R^6 and R^7 are each independently H, (C_1-C_{12})alkyl, (C_2-C_{13})acyl, or an optionally substituted phenyl or benzyl or together form a -OCR^1R^2O- group wherein each of R^1 and R^2 is independently H, a C_1-C_3 alkyl group or an optionally substituted phenyl or benzyl group; and R^8 is H, OH, an O-acyl group, a C_1,-C_4 alkyl or alkoxy group, F, Cl, Br or I, or a pharmaceutically acceptable salt thereof, which exhibit anti-P-glycoprotein activity and methods of enhancing the bioavailability of active compounds, especially orally administered compounds, by inhibition of P-glycoprotein 170 (P-gp 170) and/or CYP450 enzyme, especially CYP450 3A4 enzyme. Pharmaceutical compositions based upon these novel derivatives according to the present invention are also described herein.

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